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Full Length Article

Treatment outcomes of female germ cell tumors: The Egyptian National Cancer Institute experience

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KEYWORDS

Female germ-cell tumors;
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Abstract *Introduction:* Female germ cell tumors (GCTS) are rare tumors that carry a good prognosis.
Aim: To report the experience of the Egyptian National Cancer Institute (ENCI) in managing female GCTs.
Methods: This retrospective study included 19 females with ovarian GCTs presenting to the ENCI between 2006 and 2010.
Results: The median age was 23 years. Ovaries were the primary site in all patients. Dysgerminoma and teratoma were the predominant pathologies followed by mixed GCT in females. Unilateral ovariectomy or ovarian tumorectomy were the classic surgical procedures with R0 resection being feasible in most cases. Surveillance was adopted in six patients with stage I disease. Chemotherapy was administered in 63% of ovarian GCTs with BEP being the commonest regimen with reasonable tolerability and good response rates. The median OS and EFS were not reached. The projected 5-year OS rate was 93.8%. Both OS and EFS were better in patients responding to chemotherapy than non-responders ($p < 0.002$). Stage of disease did not significantly affect OS or EFS.
Conclusions: Female GCTs rarely affect Egyptian females. They have good prognosis.

Introduction

Non-epithelial ovarian malignancies account for about 10% of all ovarian cancers. Ovarian germ cell tumors (GCTs) represent 5% of all ovarian cancers and are mostly diagnosed in young women [1]. The yearly adjusted incidence rate is 3.7/1 000 000 [2]. In Egypt and at the population level, ovarian GCTs constitute 10% of ovarian tumors [3]. At the Egyptian National Cancer Institute, ovarian GCTs constitute 12.6% of ovarian tumors [4]. Ovarian GCTs include

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several pathologic subtypes e.g. dysgerminomas, endodermal (yolk sac) tumours, embryonal carcinomas, polyembryomas, choriocarcinomas, teratomas, and mixed GCTs [5]. The majority of GCTs (60–70%) are diagnosed at an early stage. Stage I patients have an excellent prognosis with long-term disease free status in >90% of cases [6]. Patients with stage IA grade 1 immature teratoma do not require further adjuvant chemotherapy after adequate surgical staging [7]. Also, stage IA pure dysgerminomas can be treated solely with surgery with a relatively low recurrence rate (15–25%) that can be successfully treated at the time of relapse with a high likelihood of cure [6]. Owing to their exquisite chemo-sensitivity, fertility-sparing surgery should be considered also in advanced stage disease with a cure rate of >95%. Patients should undergo debulking surgery to remove as much gross tumor as possible, but without major extensive procedures because of the high chemo-sensitivity of these tumors and the high cure [8].

Platinum-based chemotherapy regimens have been the treatment of choice and the BEP regimen is the most widely used one [9,10]. BEP is usually administered for three cycles in patients with completely resected disease and for four cycles in patients with macroscopic residual disease. However, there is no consensus as to the optimal duration of therapy [6]. Patients resistant to a cisplatin-based combination may receive vincristine–actinomycin D–cyclophosphamide (VAC) [10] or paclitaxel–gemcitabine as salvage therapy [11]. The role of secondary cytoreductive surgery in patients with recurrent or progressive ovarian GCTs remains controversial. It may have some benefits for a selected group of patients, particularly those with immature teratoma and a growing teratoma syndrome [6].

Little is known about ovarian GCTs in Egypt. Thus, we conducted this study to report the clinico-pathological features, treatments and outcomes of ovarian GCTs at the biggest Egyptian Cancer Center.

Patients and methods

This retrospective study included 19 females having ovarian GCTs at the Egyptian National Cancer Institute (NCI), Cairo University between the January 2006 and December 2010. The study was approved by the Ethics Committee of the Egyptian NCI. Relevant information was extracted from the medical records. These included subjects' demographics, clinical and pathological characteristics, treatments and their outcomes.

Statistical analyses

Statistical analyses were done using SPSS© win statistical package version 17. Survival analyses were done using the Kaplan–Meier method. Comparisons between two survival curves were done using log-rank test. A p-value <0.05 was considered statistically significant. Overall survival (OS) was defined as the time in months between the date of diagnosis and death or loss to follow up. Event-free survival (EFS) was defined as the time in months between the date of treatment and documented recurrence, progression or death.

Results

This study included 19 female patients with germ cell tumors treated at the Egyptian National Cancer Institute during the years 2006–2010.

Patients' characteristics

Age ranged between 18 and 68 years with a median of 23 years. Almost 95% of patients (18 patients) were below

Table 1 Characteristics of female patients with germ cell tumors at ENCI.

	N (%)
Total	19 (100.0)
Median age (range) years	23 (18–68)
Presentation	
Swelling	6 (31.6)
Pain	6 (31.6)
Unknown	8 (42.1)
Primary site	
Gonadal	19 (100.0)
Extra-gonadal	0 (0)
Pathology	
Dysgerminoma	9 (47.4)
Teratoma	9 (47.4)
Mixed GCT	1 (5.2)
Stage	
I	12 (63.2)
II	2 (10.5)
III	5 (26.3)
Surgery	
Ovariectomy	12 (63.2)
Ovarian cystectomy	7 (36.8)
Surgical residual	
R0	11 (57.9)
R2	1 (5.3)
Unknown	7 (36.8)
Chemotherapy	
Yes	12 (63.2)
No	6 (31.6)
Unknown	1 (5.2)
First-line chemotherapy regimen	
BEP	11 (91.7)
Paclitaxel/carboplatin	1 (7.7)
Chemotherapy response	
CR	9 (75)
PD	1 (8.3)
NA	2 (16.7)
Relapse	
RP/PALN	1 (5.3)
Pelvis and liver	1 (5.3)
Chemotherapy on relapse/progression	
BEP	2 (10.6)
Ifosfamide/epirubicin	1 (5.3)
Paclitaxel/carboplatin	1 (5.3)

Abbreviations: GCT: germ cell tumor. R0: no residual, R2: gross residual, OS: overall survival. DFS: disease free survival. PFS: progression-free survival. CR: complete remission. S.D: stable disease. P.D: progressive disease. PR: partial response OR: objective response. TAH + BSO: total abdominal hysterectomy and bilateral salpingo-oophorectomy. Ctx: chemotherapy.

the age of 40 years (Table 1). Abdomino-pelvic swelling and local pains were documented in 31.6%, each. One patient had a history of acute lymphoblastic leukemia, another one had ovarian dermoid cyst and a third one had a family history of osteosarcoma. The primary site for GCTs was the gonads in all cases. Dysgerminoma and teratoma were the predominant pathologies. All patients were surgically assessed with unilateral ovariectomy being the most common surgical procedures. It was associated with hysterectomy (i.e. TAH/BSO) in two patients with the diagnosis of malignant teratoma and stage IIIC disease having extensive peritoneal metastases outside the pelvis. One patient was 68 years old and postmenopausal and thus fertility preservation was not applicable. The other patient was 35 years and the diagnosis of GCTs was done postoperatively. Complete surgical resection (R0) was the rule. Most patients (~63%) were diagnosed early at stage I. Following surgery, 6 patients were put under surveillance and only one of them developed relapse later on and received BEP chemotherapy and achieved CR.

Chemotherapy was administered in 12 patients (63%) and BEP was the commonest regimen that was used in ~92% of cases. The median number of cycles was 4 (range, 1–6). Beyond 4 cycles, bleomycin was omitted. Toxicity was documented only in 5 patients and was mostly hematologic (neutropenia). None has documented pulmonary toxicity. At the end of chemotherapy, 75% of patients were maintained in complete remission. Two patients received second-line chemotherapy being ifosfamide/epirubicin in one patient and paclitaxel/carboplatin in other patient. One patient relapsed from CR after first-line paclitaxel/carboplatin. She received BEP and had PD.

Overall survival

The follow up period ranged between 1 and 120 months with a median of 33 months. At the last follow up visit, one patient was dead and 18 patients were alive. The median OS was not reached (Fig. 1). The 2-year OS rate was 93.8%. The impact of different confounders on OS was explored (Table 2). Response to chemotherapy was significantly associated with OS.

Event free survival (EFS)

Due to the small number of relapses in only two cases, comparison of DFS did not yield useful information. Rather, we performed a comparison based on EFS (Table 2). Events were defined as death, recurrence or progression of the disease. The median EFS was not reached (Fig. 2). The 2-year EFS rate was 73%. The impacts of different confounders on EFS were explored (Table 2). Response to chemotherapy was significantly associated with EFS.

Discussion

This retrospective study was conducted at the Egyptian NCI in a 5-year period between January 2006 and December 2010. It aimed to study female GCT's, their treatments and the impact on EFS and OS. This study included 19 female patients with ovarian GCTs.

At the NCI, ovarian germ cell tumors constituted 12.6% of ovarian tumors [4], compared to the 10% figure reported by Smith et al. [1]. In our study, the median age was 23 years (range 18–68 years), which was higher than 19 years reported

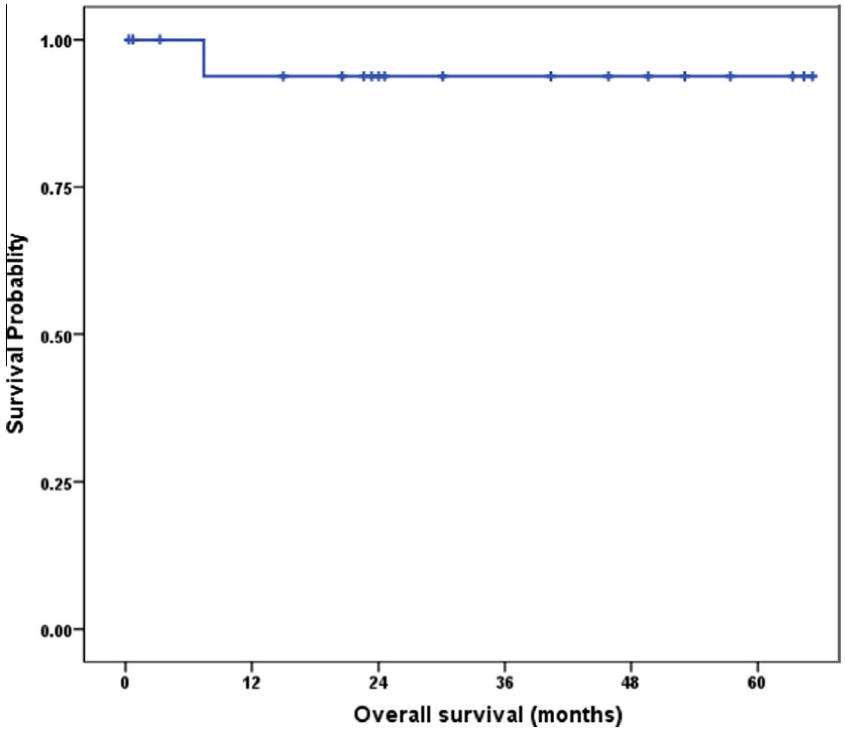

Figure 1 OS of female patients with GCTs.

Table 2 Overall and event-free survival of female germ cell tumors.

Group	*N*	Overall survival		Event-free survival	
		2YSR (SE)	*P*	2YSR (SE)	*P*
All	19	93.8 (6.1)	–	73.0 (10.4)	–
Year					
2006–2008	8	85.7 (13.2)		62.5 (17.1)	
2009–2010	11	100 (0)	0.257	80.8 (12.2)	0.361
Pathology					
Dysgerminoma	9	100 (0)		77.8 (13.9)	
Teratoma	9	85.7 (13.2)	0.285	64.8 (16.5)	0.531
Stage					
I	12	100 (0)		82.5 (11.3)	
II + III	7	83.3 (15.2)	0.197	57.1 (18.7)	0.217
Surgery					
Complete ovariectomy	10	100 (0)		80.0 (12.6)	
Partial ovariectomy	7	100 (0)	–	85.7 (13.2)	0.827

by Talukdar et al. [12]. In the first 2 decades of life, almost 70% of ovarian tumours are of germ-cell origin, and one-third of these are malignant [13].

The most common risk factor of ovarian GCT's is dysgenetic gonads so a preoperative karyotype is recommended on all pre-menarche girls because of the propensity of these tumors [14]. In the current study, Karyotyping was not performed given the retrospective nature of the study and being not the standard of care. We only documented an association with a history of acute lymphoblastic leukemia in one patient and a dermoid cyst in another one.

In the current study, teratomas and dysgerminomas were the most common pathologies. This is similar to past reports of ENCI [4] and European data showing those teratomas are the most common GCTs [6]. Clinical presentations (swelling and pain) and earlier stage at diagnosis were similar to those reported in the literature [6].

In the current study, fertility preservation surgery was achieved in 17 patients. However, two patients had TAH/BSO. One was in the postmenopausal period (68 years) while the other was 35 years of age (and completed her family with 3 children) and both were stage IIIC, with teratoma histology. This is similar to the published guidelines where unilateral salpingo-oophorectomy with preservation of the contralateral ovary and the uterus is considered the adequate surgical treatment for patients with GCTs [15,16]. In women with advanced disease (e.g. para-aortic lymph-node metastases), preservation of reproductive function is also possible, particularly if the

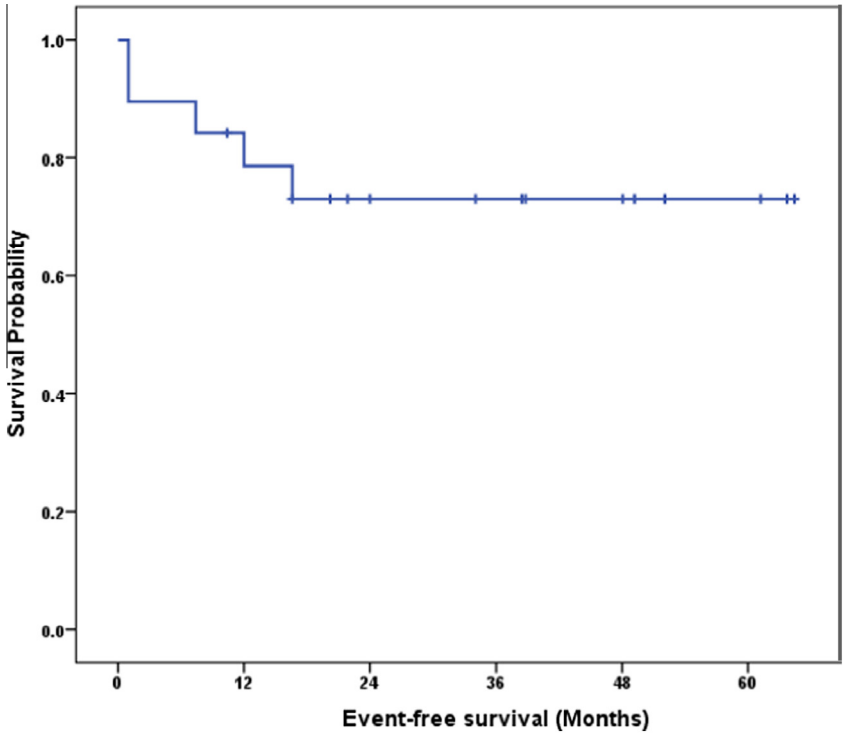

Figure 2 Event free survival (EFS) of female patients with GCTs.

contralateral ovary is normal [17,18]. Also, six patients with stage IA were kept under surveillance (3 had teratoma and 3 had dysgerminoma). This goes with the international guidelines e.g. ESMO and NCCN that advocate that stage IA pure dysgerminoma can be treated with surgery only. Recurrence rate in this group of patients is relatively low (15–25%) and they can be successfully treated at the time of relapse with a high likelihood of cure [6]. Some published data indicate that all grades of immature teratoma can be managed with close surveillance after fertility-sparing surgery, reserving chemotherapy for those cases in which post-surgery recurrence is documented [19]. Only one of the 6 followed-up cases relapsed after 17 months and achieved CR after receiving BEP for 4 cycles.

In the current study, no cases received radiotherapy despite the high radio-sensitivity of dysgerminomas. Historically, radiotherapy was used in many stage I dysgerminomas and in all patients having higher stage tumors with the field and dose determined by the stage [20]. However, this approach has many reported long-term toxicities [21,22]. In the current routine practice, radiotherapy is rarely performed since chemotherapy is equally or more effective, less toxic and less likely to compromise gonadal function [22].

Whenever indicated, platinum-based combination chemotherapy is the norm both in the early as well as in the advanced stages of ovarian GCTs with BEP ranking the first regimen [6,9]. Data from the current study fit within these norms. Chemotherapy was administered in 63% of cases; 6 had teratoma and 6 had dysgerminoma {6 cases had stage I, 2 cases had stage II, and 4 cases had stage III}. BEP was the commonest regimen used (91.7%). In the current study, two teratoma patients received second-line chemotherapy either ifosfamide/epirubicin or paclitaxel carboplatin with poor response. This reflects the poor management of women who have persistent/resistant disease after first-line chemotherapy or who progress within 4–8 weeks of completing adjuvant treatment. Results with salvage regimens and high-dose chemotherapy are poor in the setting of platinum-refractory disease [23].

Relapses were documented in two patients reflecting the good prognosis of this disease. One had stage III teratoma and received paclitaxel/carboplatin as first-line and relapsed 17 months after end of therapy. The other patient had stage IA dysgerminoma under active surveillance and relapsed 12 months after surgery. Both received BEP. Relapse site was para aortic LN's and pelvis and this is different from the usual presentation as 75% of GCT recurrences occur within the first year after initial treatment and the most common site is the peritoneal cavity, more rarely retroperitoneal lymph nodes [6].

In the current study, the median OS was not reached reflecting the good prognosis. Better survival with early compared to late stage disease was reported in the series by Rogers et al. [24]. However similar to Talukdar et al. [12], we reported lack of OS difference between early and late stage disease. The small number of cases in the current study may explain for such differences. Similar to the experience by the GOG [23], completely resected patients (R0) had better OS than those who had residual after surgery. Also, patients responding to chemotherapy have significantly better 5-year OS rates (100%) than non-responders (0%). The lower EFS of patients with stage I ovarian GCTs in the current study compared to the published figures (82.5% vs. more than 90%), may be due to the small absolute numbers. Similar to that reported to Williams et al. [25] and Williams et al. [26], patients with no residual after surgery had significantly better EFS than those with gross residual.

To the best of our knowledge, our study is the one of the very few to report on GCTs both in Egypt and worldwide. Our study has also some limitations that include being retrospective in nature and having some missing information. However, such a rare disease is best followed within such retrospective studied as prospective collection of enough number of patients will take long time and need the collaboration of many centers.

Conclusions and recommendations

The current study confirmed that FGCTs are rare tumors that affect young Egyptian patients. It also confirmed the good outcome of therapy. As shown in this study, patients with GCTs have a long survivorship and many are cured of their disease. Thus, long-term follow up is needed to follow these patients for the delayed effects of treatments. Herein, long-term follow up was suboptimal and this mandates consideration and planning to overcome. GCT patients can play a vital role in supporting other cancer patients through provision of personal experiences and encouragement. They can be good advocates for patients and the Institute. Finally, we are in need of multicenter and multinational prospective analysis of treatment options for this disease over several years with a large number of patients to understand their successes and failures.

Conflict of interest

The authors declared no conflict of interest.

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